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Remarks

The above Amendments and these Remarks are in reply to the Office Action mailed April 16, 2003.

Claims 32 and 36 have been amended to correct typographical errors, and thus are not narrowing amendments. Claims 38-44 have been amended to correct antecedents and are asserted to be not narrowing amendments.

Claims 11-16, 24-27, 30-31 and 36-46 stand rejected under 35 U.S.C. §102(b) as anticipated and/or obvious under 35 U.S.C. §103 by Sara et al. (EP 0366638; "Sara 1") alone or in combination with the instant specification at pages 1-2 to demonstrate inherency e.g., damage/loss of glial cells resulting from [due to] neural damage/injury e.g., from asphyxia/ischemia/hypoxia/stroke, and dementia disorders such as Alzheimer's addressing non-dopaminergic neurons. Office Action, page 4, paragraph 7. Additionally, "Thus, the reference treatment of neurodegenerative/neurocatabolic disease states and ischemic brain damage (e.g., stroke and asphyxia) addresses the treatment of injuries or disease which result in neural cell death." Office Action, page 7 bridging to page 8. Applicants respectfully traverse the rejections.

I. Anticipation

Applicants submit that Sara 1 does not anticipate, either expressly or inherently, the instant claims. MPEP 2131 states:

> A claim is anticipated only **if each and every element as set forth in the claim** is found, either expressly or inherently described, in a single prior art reference [references omitted]. The **identical invention must be shown in as complete detail** as is contained in the ... claim [reference omitted]. Emphasis added.

Express Anticipation

Sara 1 does not disclose "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease comprising the step of administering to said mammal a neuroprotective amount of... GPE," and therefore doesn't expressly disclose "each and every element as set forth in the claim" as required. The Examiner's statement "[t]hus, the reference treatment of

neurodegenerative/neurocatabolic disease states and ischemic brain damage (e.g., stroke and asphyxia) addresses the treatment of injuries or diseas which result in neural cell death" is unclear. Applicant does not understand whether the term "addresses" was intended to mean "anticipates." Clarification is requested. However, regardless of the meaning of the term "addresses," Applicants assert that altering neurotransmitter release induced by cellular depolarization does not necessarily include treating "injuries or disease which results in neural cell death."Thus, Applicants respectfully submit that Sara 1 does not expressly disclose each and every element of claim 11.

Inherent Anticipation

Applicants submit that Sara 1 does not inherently anticipate the instant claims. MPEP 2112 states:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference, and that **it would be so recognized** by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities.** The mere fact that a certain thing may result from a given set of circumstances is not sufficient. Emphasis added.

Firstly, Applicant's claims are drawn to "methods for treating" and not to "compositions." Applicants note that a claim is drawn to an "invention" and that invention requires a conception and reduction to practice. Applicants note that the discovery of a new effect or new use of a known composition results in a new "conception" and thus a new "invention" that is not necessarily unpatentable. Thus, Applicants' discovery of "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease comprising the step of administering to said mammal a neuroprotective amount of... GPE" is not necessarily rendered unpatentable by prior art disclosing either GPE or other uses of GPE.

Missing Elements Defeat Anticipation by Inherency

Applicants respectfully submit that there are elements missing from the prior art necessary to link a "neuromodulator" effect of Sara 1 and "neuroprotective" effects of the instant application. Specifically, the words "neuromodulator" and "neuroprotective" do not have the same plain meanings, and are used

differently in the documents themselves. Applicants enclose as Appendix I, copies of relevant pages of the Random House Unabridged Dictionary (Second Edition).

Plain Meanings of "Neuromodulator" and "Neuroprotective"

The term "neuromodulator" is a compound word made of the prefix "neuro," which is understood by persons in the art to refer to neurons. The remainder of the word is "modulator" which is subject to definition by referring to its plain meaning as defined in dictionaries.

The Random House Unabridged Dictionary (Second Edition) defines "modulator" to mean: "A person or thing that **modulates**."

The word "modulate" means:

> (1) **to regulate by or adjust to a certain measure or proportion**; soften; tone down. (2) to alter or adapt (the voice) according to the circumstances. (3) *Music* (a) to attune to a certain pitch or key. (b) to vary the volume of (tone). (4) *Telecommunications*: (a) to cause the amplitude, frequency, phase, or intensity of (a carrier wave) to vary in accordance with a sound wave or other signal, the frequency of the signal wave usually being very much lower than that of the carrier. . . Emphasis added.

Likewise, the words "neuroprotective" and "neuroprotection" are compound words consisting of the prefix "neuro" and the remainder being either "protective" or "protection." The Random House Unabridged Dictionary (Second Edition) defines "protection" to mean:

> (1) the act of protecting or the state of being protected; **preservation from injury or harm. (2) a thing, person, or group that protects**: *This vaccine is a protection against disease. . . .*" Emphasis added.

Applicants note that the dictionary does not list either as a synonym of the other. Thus, the two terms "modulate" and "protect" have different plain meanings.

Applicants submit that the word "neuromodulate" as used in Sara 1, most closely fits with the definition above "to regulate by or adjust to a certain measure or proportion." The Experiments described in Sara 1 demonstrate that GPE can "regulate or adjust" the function of neurons in brain slices by increasing or inhibiting the release of acetylcholine or by increasing the spinal reflex response.

Applicants also submit that the meaning of the claim limitation "neuroprotective amount of... GPE" means an amount of GPE that is "neuroprotective." Applicants further submit that the definition described above applies to the claim language: "preservation from injury or harm" or "a thing. . that protects."

The Terms "Neuromodulator" and "Neuroprotective" are Used Differently By Sara and by Applicants

Sara 1 uses the term "neuromodulator" in relation to results of **acute**, *in vitro* studies on brain slices (e.g., Example 2), in which GPE "is a **modulator** of neural function, thereby **stimulating or inhibiting** neural activity." Col. 1, lines 36-37; emphasis added. Sara 1 also discloses results of studies showing potentiation of spinal cord reflexes by GPE. Applicants assert that this use of "neuromodulator" is very close to the plain meaning above, namely "to regulate [neurotransmitter release or spinal reflexes] by or adjust to a certain measure or proportion [e.g., by GPE]."

In contrast, Applicants use the term "neuroprotective" refers to inhibition of cell death, as pointed out in claim 11: "A method for **protecting** glial **cells** or non-dopaminergic neural cells in a mammal **against death** from neural injury or disease comprising the step of administering to said mammal a **neuroprotective** amount of . . . GPE..." Emphasis added. Applicants submit that their use of "neuroprotection" is close to the above definition: "the act of protecting or the state of being protected; **preservation from injury or harm.** (2) **a thing, person, or group that protects**: *This vaccine is a protection against disease. . . .*" [Emphasis added, italics in original.]

For Sara 1 to inherently anticipate the instant claims, persons of ordinary skill would have to believe that **both** increasing **and** decreasing neurotransmitter release are **necessarily** linked to "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease." If the Examiner is aware of any evidence of such a reasonable belief, he is requested to provide such evidence, through either a prior art reference if available, or an Affidavit or a Declaration.

Further, Applicants invite consideration of what is not disclosed in Sara 1. Although Sara 1 discusses **potential** uses of GPE to treat dementias, Sara 1 does not provide an enabling disclosure of any such uses. Sara 1 discloses no experiments on neural survival. Sara 1 discloses (1) no *in vivo* experiments

in which GPE was used, (2) no long-term studies of any effect of GPE, (3) no experiments in which neural survival *in vivo* or *in vitro* was measured, and (4) no link between **acute** *in vitro* studies on acetylcholine release or spinal cord reflexes and survival of any cell type. Further, (5) none of the studies were described as being on brain slices from any animal that had been subjected to neural damage or disease. Thus, Applicants conclude that Sara 1 did not describe any conception and reduction to practice of any "neuroprotective" effect of GPE, and therefore cannot anticipate the instant claims.

Finally, the Examiner has provided no evidence that necessarily links "stimulating or inhibiting neural activity" with "protecting glial cells or non-dopaminergic neural cells in a mammal against **death** from neural injury or disease" as in claim 11. [Emphasis added.]

Therefore, Applicants submit that Sara 1 cannot inherently indicate that neuromodulation is useful for "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease" Although it may be possible that such an effect exists, such a **possibility** cannot sustain a rejection based on inherency. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." MPEP, Id. Thus, Applicants submit that a *prima facie* case for anticipation has not been made.

In light of the dearth of enabling disclosure about roles of GPE on neuroprotection, Applicants submit that Sara 1 cannot anticipate the instant claims.

II. Obviousness

A. Sara

Claims 11-17, 24-27, 30-31 and 36-46 stand rejected under 35 U.S.C. §103 as obvious over Sara (Sara 1).

> To establish a *prima facie* case for obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a **reasonable expectation of success**. Finally, the prior art reference must **teach or suggest all the claim limitations**. The teaching or suggestion to make the claimed combination

> and the reasonable expectation of success must both be found in the prior art, and **not based on applicant's disclosure.**

Applicants respectfully submit that the instant claims cannot be rendered obvious by Sara 1. As described above, Sara 1 discloses that GPE either "stimulates or inhibits" neural activity and can potentiate spinal cord reflexes. However, Sara 1 neither teaches nor suggests that GPE can be effective in "protecting glial cells or non-dopaminergic neural cells in a mammal against **death** from neural injury or disease." [Emphasis added.] Applicants therefore submit that Sara 1 cannot render the instant claims obvious.

Thus, at best, the experiments disclosed in Sara 1 provide an "invitation to experiment" on possible effects of GPE on brain slices from brain-damaged or brain-diseased animals, but could not have provided a reasonable basis to conclude that acute effects of GPE on neurotransmitter release inherently discloses any property of GPE to promote "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease." Rather, for Sara 1 to render the instant claims obvious, **both** potentiation and inhibition of acetylcholine release would have to relate to "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease". No link between neurotransmitter release and either disease or cell death was made in Sara 1, nor was there any disclose of conception or understanding that intervention using GPE could result in decreased neural cell death (neuroprotection).

Regarding the fact that a *prima facie* case for obviousness requires a "motive to modify the reference" and "reasonable likelihood of success," Applicants note that a subsequently published article by Sara ("The Biological Role of Truncated Insulin-like Growth Factor-1 and the Tripeptide GPE in the Central Nervous System" Annals of the New York Academy of Science; pp: 183 - 191 (1991); "Sara 2"; copy enclosed in Appendix II) addresses similar issues as in the Sara EP 0366638 ("Sara 1") but actually teaches away from Applicants' claims. In particular, Sara 2 states:

> Extensive *in vivo* studies have **not revealed any growth-promoting activity of GPE**. . . . As shown in Figure 4, no significant growth effects, including tail length and organ weights, were observed. Page 187, middle of first full paragraph.

Thus, Applicants submit that at the time of publication of Sara 2, the first inventor of Sara 1 (Sara) could not have had a reasonable belief that GPE could be a growth modulator, and thus that there would be neither a motive to try nor a reasonable likelihood of success at achieving the Applicants' invention. In the absence of a reasonable belief by the primary inventor, Applicants submit that no person of ordinary skill could have such a reasonable belief. Applicants submit that both Sara 1 and Sara 2 considered GPE to be an agent that acted on neurotransmitter receptors and not as a growth promoting hormone. Because Sara 1 was silent about any effects of GPE to promote "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease," Applicants submit that at the time of publication of Sara 1, there was neither motive nor a reasonable belief that GPE could so act.

Rather, Applicants respectfully submit that the motive and reasonable likelihood of success were provided by the Applicant's own instant disclosure.

B. Sara in View of Sibalis

Claims 11-17, 24-27 , 30-31 and 36-46 stand rejected under 35 U.S.C.§103 over Sara (Sara 1) in view of Sibalis (U.S. 5,032,109; "Sibalis").

Applicants incorporate herein the discussions presented above for Sara 1.

The Examiner stated that Sibalis teaches transdermal delivery of "polypeptides containing about three to 20 alphaamino acid units." However, Applicants can find no teaching in Sibalis and Sara 1 together of any method for "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease." Thus, the combination of Sara 1 and Sibalis does not disclose all the limitations of the pending claims with a reasonable likelihood of success, and thus cannot render Applicants' claims obvious. Applicants therefore urge the Examiner to reconsider the rejection and find the claims allowable.

C. Sara in View of Gluckman

Claims 11-16 and 18-46 stand rejected under 35 U.S.C. §103 over Sara (Sara 1) in view of Gluckman (WO 93/02695; "Gluckman").

Applicants incorporate herein the discussions presented above for Sara 1.

The Examiner stated that Gluckman teaches "a method for treatment or prevention of CNS damage caused by neurodegenerative disease and trauma which primarily causes damage to glia and/or other non-cholinergic cells in the CNS." Office Action, page 9, bottom paragraph. The Examiner also stated "It is noteworthy that the Gly-Pro-Glu peptide, as presently claimed, is derived from the N-terminal three amino acids of IGF-1 peptide." Office Action, page 10 bottom of first paragraph.

Applicants note that Gluckman does not disclose "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease, comprising administering a neuroprotective amount of ... GPE ..." as in claim 11. Nowhere in either Sara 1 nor Gluckman, nor in the combination of Sara 1 and Gluckman together, is any teaching of the use of GPE as in claim 11. Thus, the combination of Sara 1 and Gluckman does not disclose all the limitations of the pending claims with a reasonable likelihood of success, and thus cannot render Applicants' claims obvious. Although GPE is the N-terminal tripeptide of IGF-1, both Sara 2 and Gluckman teach away from GPE as a neuroprotective agent. First, Gluckman teaches that IGF-1 is neuroprotective (e.g., see Abstract and Summary of the Invention, page 3, first paragraph). Next, Sara 2 states: "The aminoterminal tripeptide of IGF-1, GPE, displays a different range of biological actions compared to truncated IGF-1. These effects are not mediated by IGF-1 receptors. As shown in Figure 3, GPE fails to cross-react with the IGF-1 receptor and does not influence the binding of either intact or truncated IGF1 to the receptor." Page 187, middle paragraph, middle section. Thus, Applicants submit that one or ordinary skill in the art would view Sara 1 in the same light as Sara 2, and when combined with Gluckman, would provide no motive to nor a reasonable believe in the success of, any study to determine whether GPE had neuroprotective properties..

Rather, Applicants submit that the instant disclosure provided the link between IGF-1, GPE and "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease, comprising administering a neuroprotective amount of ... GPE ..." as in claim 11. "To date, there has been no enabling reference in the prior art to the manipulation of the cleaved tripeptide GPE itself to prevent or treat CNS injury or disease leading to CNS damage *in vivo*." Page 3, third paragraph. Using such hindsight reconstruction to argue for unpatentability is impermissible under 35 U.S.C. §103, the MPEP

and case law. Applicants therefore urge the Examiner to reconsider the rejections and find the claims allowable.

III. Conclusions

Applicants respectfully submit that there is insufficient showing that Sara 1 either expressly or inherently anticipates or renders the instant claims obvious and that no *prima facie* for either rejection has been made. Applicants respectfully request the Examiner to provide the missing evidence necessary to make a *prima facie* showing of either anticipation or obviousness. In the absence of such evidence, either through citation of a publication or through an Affidavit or Declaration, Applicants request the Examiner to reconsider the rejections and find the claims allowable.

Further, Applicants conclude that no combination of Sara 1, Sibalis or Gluckman taught or suggested, with a reasonable likelihood of success, all limitations of the instant claims, and therefore, that no combination of those references renders the instant claim obvious. In fact, Sara 2 actually taught away from the instant claims. Because Sara 2 was published after Sara 1, Applicants conclude that any interpretation of Sara 1 to teach "protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease, comprising administering a neuroprotective amount of ... GPE ..." is not supported.

In light of the above, it is respectfully submitted that all of the claims now pending in the subject patent application should be allowable, and a Notice of Allowance is requested. The Examiner is respectfully requested to telephone the undersigned if he [she] can assist in any way in expediting issuance of a patent.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit

Account No. 06-1325 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: July 10, 2003

By: D. Benjamin Borson

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APPENDIX I

Copies of Relevant Pages from

Random House Unabridged Dictionary (Second Edition)

RANDOM HOUSE UNABRIDGED DICTIONARY

Second Edition

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stic variation.

Mo·der·sohn-Beck·er (mō′dən zōn bek′ən), *n.* **Pau·l** (pou′lä), 1876–1907, German painter

mod·est (mod′ist), *adj.* **1.** having or showing a moderate or humble estimate of one's merits, importance, etc.; free from vanity, egotism, boastfulness, or great pretensions. **2.** free from ostentation or showy extravagance: *a modest house.* **3.** having or showing regard for the decencies of behavior, speech, dress, etc.; decent: *a modest neckline on a dress.* **4.** limited or moderate in amount, extent, etc.: *a modest increase in salary.* [1555–65; < L *modestus* restrained, decorous, equiv. to *modes-*, of **modus*, an s-stem akin to *modus* MODE[1], perh. < *medos*, with the vowel of *modus*; cf. *moderārī* to MODERATE, from the same n.: stem) + *-tus* adj. suffix] **—mod′est·ly,** *adv.*

—Syn. 1. retiring, unassuming. **1, 2.** unpretentious, unobtrusive. **3.** pure, virtuous. MODEST, DEMURE, PRUDISH imply conformity to propriety and decorum, and a distaste for anything coarse or loud. MODEST implies a becoming shyness, sobriety, and proper behavior: *a modest, self-respecting person.* DEMURE implies a bashful, quiet simplicity, staidness, and decorum; but can also indicate an assumed or affected modesty: *a demure young chorus girl.* PRUDISH suggests an exaggeratedly self-conscious modesty or propriety in behavior or conversation of one who wishes to be thought of as easily shocked and who often is intolerant: *a prudish objection to a harmless remark.* **—Ant. 3.** bold, coarse.

Mo·des·to (mə des′tō), *n.* a city in central California. 106,105.

mod·es·ty (mod′ə stē), *n., pl.* **-ties. 1.** the quality of being modest; freedom from vanity, boastfulness, etc. **2.** regard for decency of behavior, speech, dress, etc. **3.** simplicity; moderation. [1525–35; < L *modestia.* See MODEST, -Y[3]]

mod′esty pan′el, a panel across the front of a desk, esp. an office desk, designed to conceal the legs of a person seated at it.

MODFET (mod′fet′), *n. Electronics.* modulation-doped field effect transistor.

ModGk, Modern Greek. Also, **Mod. Gk., Mod. Gr.**

ModHeb, Modern Hebrew. Also, **Mod. Heb.**

mod·i·cum (mod′i kəm), *n.* a moderate or small amount: *He hasn't even a modicum of common sense.* [1425–75; late ME < L, n. use of neut. of *modicus* moderate, equiv. to *modi-*, comb. form of *modus* limit (see MODE[1]) + *-cus* adj. suffix]

modif., modification.

mod·i·fi·cand (mod′ə fi kand′), *n. Gram.* a word that is modified, or qualified, by another. In *red books, books* is a modificand. [1825–35; < L *modificandum* (a thing) to be measured or limited, ger. of *modificare* to MODIFY]

mod·i·fi·ca·tion (mod′ə fi kā′shən), *n.* **1.** an act or instance of modifying. **2.** the state of being modified; partial alteration. **3.** a modified form; variety. **4.** *Biol.* a change in a living organism acquired from its own activity or environment and not transmitted to its descendants. **5.** limitation or qualification. **6.** *Gram.* **a.** the use of a modifier in a construction, or of modifiers in a class of constructions or in a language. **b.** the meaning of a modifier, esp. as it affects the meaning of the word or other form modified: *Limitation is one kind of modification.* **c.** a change in the phonological shape of a morpheme, word, or other form when it functions as an element in a construction, as the change of *not* to *-n't* in *doesn't.* **d.** an adjustment in the form of a word as it passes from one language to another. [1495–1505; < L *modificātiōn-* (s. of *modificātiō*), equiv. to *modificāt(us)* (ptp. of *modificāre;* see MODIFY) + *-iōn-* -ION]

mod·i·fi·ca·to·ry (mod′ə fi kə tôr′ē, -tōr′ē), *adj.* modifying. Also, **mod′i·fi·ca′tive.** [1815–25; < L *modificāt(us)* (see MODIFICATION) + -ORY[1]]

mod′ified Amer′ican plan′, (in hotels) a system of paying a single fixed rate that covers room, breakfast, and one other meal, usually dinner. *Abbr.:* MAP Cf. **American plan, demi-pension, European plan.**

mod·i·fi·er (mod′ə fī′ər), *n.* **1.** a person or thing that modifies. **2.** *Gram.* **a.** a word, phrase, or sentence element that limits or qualifies the sense of another word, phrase, or element in the same construction. **b.** the immediate constituent of an endocentric construction that is not the head. [1575–85; MODIFY + -ER[1]] **—Usage.** See **dangling participle, misplaced modifier.**

mod·i·fy (mod′ə fī′), *v.,* **-fied, -fy·ing.** *—v.t.* **1.** to change somewhat the form or qualities of; alter partially; amend: *to modify a contract.* **2.** *Gram.* (of a word, phrase, or clause) to stand in a syntactically subordinate relation to (another word, phrase, or clause), usually with descriptive, limiting, or particularizing meaning; be a modifier. In *a good man, good* modifies *man.* **3.** to be the modifier or attribute of. **4.** to change (a vowel) by umlaut. **5.** to reduce or lessen in degree or extent; moderate; soften: *to modify one's demands.* *—v.i.* **6.** to be or become modified. [1350–1400; ME *modifien* < MF *modifier* < L *modificāre* to impose a rule or pattern, regulate, restrain. See MODE[1], -IFY] **—mod′i·fi′a·ble,** *adj.* **—mod′i·fi′a·bil′i·ty, mod′i·fi′a·ble·ness,** *n.*

—Syn. 1. vary, adjust, shape, reform. **5.** MODIFY, QUALIFY, TEMPER suggest altering an original statement, condition, or the like, so as to avoid anything excessive or extreme. To MODIFY is to alter in one or more particulars, generally in the direction of leniency or moderation: *to modify demands, rules.* To QUALIFY is to restrict or limit by exceptions or conditions: *to qualify one's praise.*

VL **mutiliōnem,* var. of **mutuliōnem,* acc. of **mūtuliō.* See MUTULE, -ION]

mo·di·o·lus (mō dī′ə ləs, mə-), *n., pl.* **-li** (-lī′). *Anat.* the central, conical axis of the cochlea of the ear. [1685–95; < NL, L: nave of a wheel bucket, drinking vessel, equiv. to *modi(us)* a dry measure (perh. deriv. of *modus* MODE[1]) + *-olus* -OLE[1]] **—mo·di′o·lar,** *adj.*

mod·ish (mō′dish), *adj.* in the current fashion; stylish. [1650–60; MODE[2] + -ISH[1]] **—mod′ish·ly,** *adv.* **—mod′ish·ness,** *n.*

—Syn. smart, chic, fashionable, trendy.

mo·diste (mō dēst′; *Fr.* mô dēst′), *n., pl.* **-distes** (-dēsts′; *Fr.* -dēst′). *Older Use.* a female maker of or dealer in women's fashionable attire. [1830–40; < F; see MODE[2], -IST]

Mo·djes·ka (mō jes′kə), *n.* **He·le·na** (he lā′nə), (*Helena Opid Modrzejewska*), 1840–1909, Polish actress, in U.S. after 1876.

Mo·doc (mō′dok), *n., pl.* **-docs,** (esp. *collectively*) **-doc.** a member of an American Indian people belonging to the Lutuamian group and ranging from southern Oregon to northern California.

mo′dock wool′ (mō′dok). See **territory wool.** [special use of MODOC]

mod. praesc., (in prescriptions) in the manner prescribed; as directed. [< L *modō praescrīptō*]

Mo·dred (mō′drid), *n. Arthurian Romance.* the nephew and treacherous killer of Arthur. Also, **Mordred.**

mod·u·lar (moj′ə lər), *adj.* **1.** of or pertaining to a module or a modulus. **2.** composed of standardized units or sections for easy construction or flexible arrangement: *a modular home; a modular sofa.* **3.** *Math.* (of a lattice) having the property that for any two elements with one less than the other, the union of the smaller element with the intersection of the larger element and any third element of the lattice is equal to the intersection of the larger element with the union of the smaller element and the third element. **4.** *Computers.* composed of software or hardware modules that can be altered or replaced without affecting the remainder of the system. *—n.* **5.** something, as a house or piece of furniture, built or organized in self-contained units or sections. **6.** a self-contained unit or item, as of furniture, that can be combined or interchanged with others like it to create different shapes or designs. [1790–1800; < NL *modulāris.* See MODULE, -AR[1]]

mod′ular arith′metic, arithmetic in which numbers that are congruent modulo a given number are treated as the same. Cf. **congruence** (def. 2), **modulo, modulus** (def. 2b). [1955–60]

mod·u·lar·i·ty (moj′ə lar′i tē, mod′yə-), *n.* the use of individually distinct functional units, as in assembling an electronic or mechanical system. [1935–40; MODULAR + -ITY]

mod·u·lar·ize (moj′ə lə rīz′), *v.t.,* **-ized, -iz·ing.** to form or organize into modules, as for flexibility. Also, esp. *Brit.,* **mod′u·lar·ise′.** [1955–60; MODULAR + -IZE] **—mod′u·lar·i·za′tion,** *n.*

mod·u·late (moj′ə lāt′), *v.,* **-lat·ed, -lat·ing.** *—v.t.* **1.** to regulate by or adjust to a certain measure or proportion; soften; tone down. **2.** to alter or adapt (the voice) according to the circumstances, one's listener, etc. **3.** *Music.* **a.** to attune to a certain pitch or key. **b.** to vary the volume of (tone). **4.** *Telecommunications.* to cause the amplitude, frequency, phase, or intensity of (a carrier wave) to vary in accordance with a sound wave or other signal, the frequency of the signal wave usually being very much lower than that of the carrier. *—v.i.* **5.** *Telecommunications.* **a.** to modulate a carrier wave. **b.** *CB Slang.* to talk; visit: *Enjoyed modulating with you.* **6.** *Music.* to pass from one key to another: *to modulate abruptly from A to B flat.* [1550–60; < L *modulātus* (ptp. of *modulārī* to regulate (sounds), set to music, play an instrument). See MODULE, -ATE[1]] **—mod·u·la·bil·i·ty** (moj′ə lə bil′i tē), *n.* **—mod′u·la′tive, mod·u·la·to·ry** (moj′ə lə tôr′ē, -tōr′ē), *adj.*

—Syn. 2. temper, control.

mod·u·la·tion (moj′ə lā′shən, mod′yə-), *n.* **1.** the act of modulating. **2.** the state of being modulated. **3.** *Music.* transition from one key to another. **4.** *Gram.* **a.** the use of a particular distribution of stress or pitch in a construction, as the use of rising pitch on *here* in *John is here?* **b.** the feature of a construction resulting from such use. [1350–1400; ME < L *modulātiōn-* (s. of *modulātiō*) rhythmical measure. See MODULATE, -ION]

mod·u·la·tor (moj′ə lā′tər), *n.* **1.** a person or thing that modulates. **2.** *Telecommunications.* a device for modulating a carrier wave. [1490–1500; < L *modulātor;* see MODULATE, -TOR]

mod·ule (moj′o͞ol), *n.* **1.** a separable component, fre-

any two operators and any group element th[...] having the first operator act on the elemen[...] second element, and the second operator act [...] ond element is equal to the result of having a[...] erator, formed by adding or multiplying the [...] tors, act on the first element. Cf. **ring**[1] (d[...] *Computers.* **a.** part of a program that perform[...] function. **b.** an interchangeable, plug-in hard[...] [1555–65; < L *modulus;* see MODULUS]

mod·u·lo (moj′ə lō′), *adv. Math.* with re[...] modulus: *6 is congruent to 11, modulo 5.* [18[...] NL *modulō,* abl. of L *modulus* MODULUS]

mod·u·lus (moj′ə ləs), *n., pl.* **-li** (-lī′). **1.** *Ph*[...] efficient pertaining to a physical property. **2**[...] that number by which the logarithms in one [...] multiplied to yield the logarithms in another. [...] tity by which two given quantities can be [...] yield the same remainders. **c.** See **absol**[...] [1555–65; < L: a unit of measure; see MODE[1],

mod′ulus of elastic′ity, *Physics.* any of [...] efficients of elasticity of a body, expressing th[...] tween a stress or force per unit area that acts [...] the body and the corresponding fractional d[...] caused by the stress. Also called **coefficient** [...] **ity, elastic modulus.** [1800–10]

mod′ulus of rigid′ity, *Physics.* See **shea**[...] [1875–80]

mod′ulus of tor′sion, *Physics.* See **shea**[...]

mo·dus op·e·ran·di (mō′dəs op′ə ran′dē[...] mō′dəs ō′pe rän′dē), *pl.* **mo·di op·e·ran·di** (mō′dī op′ə ran′dē, mō′dī op′ə ran′dī; *Lat.* mō′dē [...] dē). mode of operating or working. [164[...] *modus operandi*]

mo·dus vi·ven·di (mō′dəs vi ven′dē, -dī), **vi·ven·di** (mō′dē vi ven′dē, mō′dī vi ven′dī[...] ner of living; way of life; lifestyle. **2.** a tem[...] rangement between persons or parties pendir[...] ment of matters in debate. [1875–80 < L *mo*[...] mode of living]

Moe (mō), *n.* a male given name, form of **Moses.**

Moe·bi·us (mœ′bē əs, mā′-, mō′-), *n.* **Aug**[...] **nand.** See **Möbius, August Ferdinand.**

Moe·rae (mē′rē), *n.pl. Class. Myth.* the Fat[...]

Moe·si·a (mē′shē ə), *n.* an ancient countr[...] rope, S of the Danube and N of ancient Thrac[...] edonia: later a Roman province.

Moe·so·goth (mē′sō goth′, -sə-), *n.* one of [...] tianized Goths who settled in Moesia in the 4[...] A.D.

Moe·so·goth·ic (mē′sō goth′ik, -sə-), *adj.* [...] taining to the Moesogoths or their language [...] GOTH + -IC]

mo·fette (mō fet′; *Fr.* mō fet′), *n.* **1.** a no[...] nation, consisting chiefly of carbon dioxide [...] from the earth in regions of nearly extinct v[...] tivity. **2.** one of the openings or fissures from [...] emanation issues. Also, **mof·fette′.** [1815–25 [...] *moffetta* (Neapolitan *mufeto*), equiv. to *muff*[...] It *mofa*) mould (< Langobardic; cf. G *Muff* [...] MHG *müffeln* to give off a foul smell) + *-ett*[...]

mog[1] (mog), *v.,* **mogged, mog·ging.** *Dial.* [...] move on, depart, or decamp (usually fol. by [...] **2.** to walk or move along gently, slowly, an[...] *—v.t.* **3.** to cause to go from one place t[...] [1665–75; M(OVE) + (J)OG[1]]

mog[2] (mog), *n.* moggy. [by shortening]

Mo·ga·di·shu (mō′gä dē′sho͞o), *n.* a seap[...] the capital of Somalia, in the S part. 400,000. I[...] **ga·di·scio** (mō′gä dē′shō).

Mog·a·dor (mog′ə dôr′, -dōr′; *Fr.* mō gȧ d[...] former name of **Essaouira. 2.** (*l.c.*) Also, **mo**[...] a ribbed fabric of silk or rayon warp and cott[...] filling, used for neckties.

Mo·gen Da·vid (mō′gən dā′vid; *Seph. Heb.* [...] dä vēd′; *Ashk. Heb.* mō′gən dō′vid), *Juda*[...] **Star of David.** [1900–05]

mog·gy (mog′ē), *n., pl.* **-gies.** *Brit. Inform*[...] Also, **mog.** [1815–25; said to be orig. Cockney [...] derivations from dial. (W Midlands) *Moggy* pe[...] a calf, or from personal name MAGGIE, are d[...]

Mo·ghul (mō′gəl, -gul, mō gul′), *n., adj.* M[...] 1, 2, 6).

Mo·gi das Cru·zes (mōō zhē′ däs kro͞o′z[...] in SE Brazil, E of São Paulo. 111,554.

mog·i·la·li·a (moj′ə lā′lē ə, -lāl′yə), *n.* any [...] fect, as stuttering or stammering. Also, **mollal**[...] 80; < Gk *mogilál(os)* hardly talking (*mógi(s)* [...] culty + *lálos* babbling) + *-ia* -IA]

Mo·gi·lev (mō′gi lef′; *Russ.* mə gyi lyôf′), *n.* [...] E Byelorussia (Belarus), on the Dnieper. 359,0[...]

mo·go (mō′gō), *n., pl.* **-gos.** *Australian.* [...] hatchet used by the Aborigines. [1815–25; [...] *mu·gu*]

Mo·gol·lon (mō′gə yōn′), *n.* **1.** an extensi[...] or mesa in central Arizona; the southwestern [...] the Colorado Plateau. **2.** a mountain range [...] Mexico. *—adj.* **3.** *Archaeol.* of or pertaining to [...] indian culture of southeastern Arizona and so[...] New Mexico 100 B.C.–A.D. 1000, characteriz[...] houses also used for burials and a distinctive [...] white pottery decorated with human and anim[...]

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e *prospectus carefully.* 2. a brochure or other describing the major features, attractions, or a place, institution, or business to prospective mts, owners, or members. [1770–80; < L *prō-* look, view, equiv. to *prōspec-*, s. of *prōspicere* + *-spicere*, comb. form of *specere* to look) + of v. action]

(pros′per), *v.i.* 1. to be successful or fortu- financial respects; thrive; flourish. —*v.t.* 2. make successful or fortunate. [1425–75; late en < L *prosperāre* to make happy, deriv. of gosperous]
See **succeed**. —**Ant.** 1. fail.

ty (pro sper′i tē), *n., pl.* **-ties.** 1. a success- ing, or thriving condition, esp. in financial od fortune. 2. **prosperities,** prosperous cir- [1175–1225; ME *prosperite* < OF < L *pro-* PROSPEROUS, -ITY]

(pros′pə rō′), *n.* (in Shakespeare's *The* e exiled Duke of Milan, who is a magician.

us (pros′per əs), *adj.* 1. having or charac- inancial success or good fortune; flourishing: *a prosperous business.* 2. well-to-do or *rosperous family.* 3. favorable or propitious. te ME < L *prosperus*] —**pros′per·ous·ly,** *′per·ous·ness, n.*
thriving. 2. wealthy, rich. 3. fortunate, cious.

a (*Gk.* prôs′fō rä; *Eng.* pros′fə rä′, -far ə), *n.* antidoron. [1870–75; < Gk *prosphorá* an . a bringing to, applying, equiv. to *pros-* to- *rá* something carried (verbid of *phérein* to

on (*Gk.* prôs′fô rōn; *Eng.* pros′fə ron′, *Eastern Ch.* an uncut loaf of altar bread be- secrated. [< Gk *prósphoron*, n. use of neut. s useful, fitting, deriv. of *prosphorá* PROS-

), *v.t. Scot. and North Eng.* to exhibit pride ss; put on airs. [perh. Scots var., in v. use, —**pross′er,** *n.* —**pross′y,** *adj.*

), *n. Slang.* prostitute. [by shortening and

ros′ər), *n.* **Gabriel,** 1775?–1800, U.S. leader ful slave revolt.

), *interj.* prosit. [by contr.]

clin (pros′tə sī′klin), *n. Biochem.* a pros- $_{20}H_{32}O_5$, that specifically inhibits the forma- l clots. [1975–80; PROSTA(TE) + CYCL(IC) + model of PROSTAGLANDIN]

n·din (pros′tə glan′din), *n.* 1. *Biochem.* ss of unsaturated fatty acids that are in- contraction of smooth muscle, the control ion and body temperature, and many other functions. 2. *Pharm.* any commercial of this substance. [1935–40; PROSTA(TE) + N[2]]

rŏ′stas), *n., pl.* **pro·sta·des** (prō stā′dēz). al architecture) an antechamber or vesti- a classical temple) the area included be- ades. [< Gk *prostás* lit., that which stands OSTASIS)]

(prō stā′sis), *n., pl.* **-ses** (-sēz). (in a classi- pronaos or prostas before a cella. [< Gk PRO-[2], STASIS]

ros′tāt), *Anat.* —*adj.* 1. Also, **pros·tat·ic** of or pertaining to the prostate gland. —*n.* ate gland. [1640–50; < NL *prostata* < Gk standing before. See PRO-[2], -STAT]

to·my (pros′tə tek′tə mē), *n., pl.* **-mies.** on of part or all of the prostate gland. STATE + -ECTOMY]

land′, *Anat.* an organ that surrounds the les at the base of the bladder, comprising a tion, which controls the release of urine, ar portion, which secretes an alkaline fluid up part of the semen and enhances the ertility of sperm. [1830–40]

′tricle, *Anat.* a small pouch near the l that opens into the urethra. [1920–25]

(pros′tə tiz′əm), *n.* symptoms of pros- esp. obstructed urination, arising from be- nent or chronic disease of the prostate 1900; PROSTATE + -ISM]

(pros′tə tī′tis), *n. Pathol.* inflammation e gland. [PROSTATE + -ITIS]

n (prō stûr′nəm), *n., pl.* **-na** (-nə), **-nums.** terite of the prothorax of an insect. [1820– PRO-[1], STERNUM] —**pro·ster′nal,** *adj.*

tion and fitting of prosthetic devices, esp. artificial limbs. [1890–95; see PROSTHETIC, -ICS]

pros·the·tist (pros′thi tist), *n.* a person skilled in making or fitting prosthetic devices. [1900–05; PROS- THET(ICS) + -IST]

pros·thi·on (pros′thē on′), *n. Craniom.* the most for- ward projecting point of the anterior surface of the upper jaw, in the midsagittal plane. [1920–25; < Gk *prósthion*, neut., of *prósthios* frontal, akin to *prósthen* forward] —**pros′thi·on′ic,** *adj.*

pros·tho·don·tics (pros′thə don′tiks), *n.* (*used with a singular v.*) the branch of dentistry that deals with the restoration and maintenance of oral function by the re- placement of missing teeth and other oral structures by artificial devices. Also, **pros·tho·don·tia** (pros′thə don′- shə, -shē ə). [1945–50; PROSTH(ESIS) + -ODONT + -ICS]

pros·tho·don·tist (pros′thə don′tist), *n.* a specialist in prosthodontics. [1915–20; PROSTHODONT(ICS) + -IST]

pros·tie (pros′tē), *n. Slang.* a prostitute. [PROS- T(ITUTE) + -IE]

Pro·stig·min (prō stig′min), *Pharm., Trademark.* a brand of neostigmine.

pros·ti·tute (pros′ti to͞ot′, -tyo͞ot′), *n., v.,* **-tut·ed, -tut·ing.** —*n.* 1. a woman who engages in sexual intercourse for money; whore; harlot. 2. a man who engages in sex- ual acts for money. 3. a person who willingly uses his or her talent or ability in a base and unworthy way, usually for money. —*v.t.* 4. to sell or offer (oneself) as a prosti- tute. 5. to put to any base or unworthy use: *to prostitute one's talents.* [1520–30; < L *prōstitūta*, n. use of fem. of *prōstitūtus*, ptp. of *prōstituere* to expose (for sale), equiv. to *prō-* PRO-[1] + *-stitu-*, comb. form of var. s. of *statuere* to cause to stand + *-tus* ptp. suffix; see STATUS] —**pros′ti·tu′tor,** *n.*
—**Syn.** 1. call girl, streetwalker, courtesan; trollop, strumpet.

pros·ti·tu·tion (pros′ti to͞o′shən, -tyo͞o′-), *n.* 1. the act or practice of engaging in sexual intercourse for money. 2. base or unworthy use, as of talent or ability. [1545–55; < LL *prostitūtiōn-* (s. of *prōstitūtiō*). See PROS- TITUTE, -ION]

pro·sto·mi·ate (prō stō′mē āt′), *adj.* having a pro- stomium. [1885–90; PROSTOMI(UM) + -ATE[1]]

pro·sto·mi·um (prō stō′mē əm), *n., pl.* **-mi·a** (-mē ə). the unsegmented, preoral portion of the head of certain lower invertebrates. [1865–70; < NL < Gk *prostómion* mouth. See PRO-[2], STOMA, -IUM] —**pro·sto′mi·al,** *adj.*

pro·sto·on (prō stō′on), *n., pl.* **-sto·a** (-stō′ə). (in clas- sical architecture) a portico. [< Gk *próstoon*; see PRO-[2], STOA]

pros·trate (pros′trāt), *v.,* **-trat·ed, -trat·ing,** *adj.* —*v.t.* 1. to cast (oneself) face down on the ground in hu- mility, submission, or adoration. 2. to lay flat, as on the ground. 3. to throw down level with the ground. 4. to overthrow, overcome, or reduce to helplessness. 5. to reduce to physical weakness or exhaustion. —*adj.* 6. lying flat or at full length, as on the ground. 7. lying face down on the ground, as in token of humility, sub- mission, or adoration. 8. overthrown, overcome, or helpless: *a country left prostrate by natural disasters.* 9. physically weak or exhausted. 10. submissive. 11. ut- terly dejected or depressed; disconsolate. 12. *Bot.* (of a plant or stem) lying flat on the ground. [1350–1400; (adj.) ME *prostrat* < L *prōstrātus*, ptp. of *prōsternere* to throw prone, equiv. to *prō-* PRO-[1] + *strā-*, var. s. of *ster- nere* to stretch out + *-tus* ptp. suffix; (v.) ME *prostraten*, deriv. of the adj.] —**pros·tra·tive** (pros′trə tiv), *adj.* —**pros′tra·tor,** *n.*
—**Syn.** 6. prone, supine, recumbent.

pros·tra·tion (pro strā′shən), *n.* 1. the act of pros- trating. 2. the state of being prostrated. 3. extreme mental or emotional depression or dejection: *nervous prostration.* 4. extreme physical weakness or exhaus- tion: *heat prostration.* [1520–30; < LL *prōstrātiōn-* (s. of *prōstrātiō*) a lying prone. See PROSTRATE, -ION]

pro·style (prō′stīl), *Archit.* —*adj.* 1. (of a classical temple) having a portico on the front with the columns in front of the antae. —*n.* 2. a prostyle building or por- tico. [1690–1700; (adj.) < L *prostȳlos* < Gk *próstylos* with pillars in front, equiv. to *pro-* PRO-[2] + *-stylos* -STYLE[2]; (n.) < Gk *próstylon*, n. use of neut. of *próstylos*]

pros·y (prō′zē), *adj.,* **pros·i·er, pros·i·est.** 1. of the nature of or resembling prose. 2. prosaic; dull, tedious, wearisome, or commonplace. [1805–15; PROSE + -Y[1]] —**pros′i·ly,** *adv.* —**pros′i·ness,** *n.*

pro·syl·lo·gism (prō sil′ə jiz′əm), *n. Logic.* a syllo- gism the conclusion of which is used as a premise of an- other syllogism; any of the syllogisms included in a poly- syllogism except the last. Cf. **episyllogism.** [1575–85; < ML *prosyllogismus* < Gk *prosyllogismós*. See PRO-[2], SYL- LOGISM]

See PROTO-, ANTAGONIST] —**pro·tag′o·nism,** *n.*

Pro·tag·o·ras (prō tag′ər əs), *n.* c480–c421 B.C., Greek Sophist philosopher. —**Pro·tag·o·re·an** (prō- tag′ə rē′ən), *adj.* —**Pro·tag′o·re′an·ism,** *n.*

prot·a·mine (prō′tə mēn′, prō tam′in), *n. Biochem.* any of a group of arginine-rich, strongly basic proteins that are not coagulated by heat, occurring primarily in the sperm of fish. [1870–75; PROT- + AMINE]

prot·a·nom·a·ly (prōt′n om′ə lē), *n. Ophthalm.* a de- fect of vision characterized by a diminished response of the retina to red. [1935–40; PROT- + ANOMALY] —**prot′- a·nom′a·lous,** *adj.*

pro·ta·no·pi·a (prōt′n ō′pē ə), *n. Ophthalm.* a defect of vision in which the retina fails to respond to red or green. [1900–05; < NL; see PROT-, AN-[1], -OPIA] —**pro- ta·nop·ic** (prōt′n op′ik), *adj.*

prot·a·sis (prot′ə sis), *n., pl.* **-ses** (-sēz′). 1. the clause expressing the condition in a conditional sentence, in English usually beginning with *if.* Cf. **apodosis.** 2. the first part of an ancient drama, in which the characters are introduced and the subject is proposed. Cf. **catasta- sis, catastrophe** (def. 4), **epitasis.** 3. (in Aristotelian logic) a proposition, esp. one used as a premise in a syllo- gism. [1610–20; < LL: introduction in a drama < Gk *prótasis* proposition, lit., a stretching forward, equiv. to *pro-* PRO-[2] + *tásis* a stretching (ta-, verbid s. of *teínein* to stretch + *-sis* -SIS)]

pro·te·an (prō′tē ən, prō tē′-), *adj.* 1. readily assum- ing different forms or characters; extremely variable. 2. changeable in shape or form, as an amoeba. 3. (of an actor or actress) versatile; able to play many kinds of roles. 4. (*cap.*) of, pertaining to, or suggestive of Pro- teus. [1590–1600; PROTE(US) + -AN] —**pro′te·an·ism,** *n.*

pro·te·ase (prō′tē ās′, -āz′), *n. Biochem.* any of a group of enzymes that catalyze the hydrolytic degrada- tion of proteins or polypeptides to smaller amino acid polymers. [1900–05; PROTE(IN) + -ASE]

pro·tect (prə tekt′), *v.t.* 1. to defend or guard from attack, invasion, loss, annoyance, insult, etc.; cover or shield from injury or danger. 2. *Econ.* to guard (the in- dustry or an industry of a nation) from foreign competi- tion by imposing import duties. 3. to provide funds for the payment of (a draft, note, etc.). —*v.i.* 4. to provide, or be capable of providing, protection: *a floor wax that protects as well as shines.* [1520–30; < L *prōtēctus*, ptp. of *prōtegere* to cover in front, equiv. to *prō-* PRO-[1] + *teg-*, s. of *tegere* to cover (akin to TOGA, THATCH) + *-tus* ptp. suffix] —**pro·tect′i·ble, pro·tect′a·ble,** *adj.* —**pro- tect′i·bil′i·ty, pro·tect′a·bil′i·ty,** *n.*
—**Syn.** 1. screen, shelter. See **defend.** —**Ant.** 1. at- tack.

pro·tect·ant (prə tek′tənt), *n.* a substance, as a chemical spray, that provides protection, as against in- sects, frost, rust, etc.; protective agent. [1660–70, for an earlier sense; PROTECT + -ANT]

pro·tec·tee (prə′tek tē′, prə tek-), *n.* a person, as a head of state, for whom official protection is provided. [1595–1605; PROTECT + -EE]

pro·tect·ing (prə tek′ting), *adj.* providing protection or shelter. [1620–30; PROTECT + -ING[2]] —**pro·tect′ing- ly,** *adv.* —**pro·tect′ing·ness,** *n.*

pro·tec·tion (prə tek′shən), *n.* 1. the act of protecting or the state of being protected; preservation from injury or harm. 2. a thing, person, or group that protects: *This vaccine is a protection against disease.* 3. patronage. 4. *Insurance.* coverage (def. 1). 5. *Informal.* a. money paid to racketeers for a guarantee against threatened vio- lence. b. bribe money paid to the police, politicians, or other authorities for overlooking criminal activity. 6. *Econ.* protectionism. 7. a document that assures safety from harm, delay, or the like, for the person, persons, or property specified in it. 8. *Archaic.* a document given by the U.S. customs authorities to a sailor traveling abroad certifying that the holder is a citizen of the U.S. [1275–1325; ME *protecio(u)n* < LL *prōtēctiōn-* (s. of *prōtēctiō*) a covering in front. See PROTECT, -ION] —**pro- tec′tion·al,** *adj.*
—**Syn.** 1. security, refuge, safety. 2. guard, defense, shield, bulwark. See **cover.** 3. aegis, sponsorship. 7. pass, permit.

pro·tec·tion·ism (prə tek′shə niz′əm), *n.* 1. *Econ.* the theory, practice, or system of fostering or developing domestic industries by protecting them from foreign competition through duties or quotas imposed on impor- tations. 2. any program, policy, or system of laws that seeks to provide protection for property owners, wildlife,

CONCISE PRONUNCIATION KEY: act, cāpe, dâre, pärt; set, ēqual; if, īce; ox, ōver, ôrder, oil, bo͝ok, bo͞ot, out; up, ûrge; child; sing; shoe; thin, *th*at; zh as in *treasure*. ə = a as in *alone*, e as in *system*, i as in *easily*, o as in *gallop*, u as in *circus*; ′ as in *fire* (fī′ər), *hour* (ou′ər). l and n can serve as syllabic consonants, as in *cradle* (krād′l), and *button* (but′n). See the full key inside the front cover.

adj.	**pro′-O·ri·en′tal,** *adj., n.*	**pro-Pan′a·ma′,** *adj.*	**pro′pa·tri·ot′ic,** *adj.*	**pro-Phil′ip·pine′,** *adj.*
lj.	**pro-or′tho·dox′,** *adj.*	**pro′-Pan·a·ma′ni·an,** *adj., n.*	**pro-pa′tri·ot·ism,** *n.*	**pro-Pol′ish,** *adj.*
adj.	**pro-or′tho·dox′y,** *adj.*	**pro-pa′pist,** *n., adj.*	**pro-pa′tron·age,** *adj.*	**pro-pol′i·tics,** *adj.*
ian, *adj., n.*	**pro-pac′i·fism,** *n.*	**pro-Par′a·guay′,** *adj.*	**pro-pay′ment,** *adj.*	**pro′-Por·tu·guese′,** *adj., n.,*
dj.	**pro-pac′i·fist,** *n., adj.*	**pro′-Par·a·guay′an,** *adj., n.*	**pro′-Pe·ru′vi·an,** *adj., n.*	*pl.* **-guese.**

the environment, etc. [1855–60; PROTECTION + -ISM]
—**pro·tec/tion·is/tic,** *adj.*
—**pro·tec/tion·ist,** *n., adj.*

pro·tec·tive (prə tek/tiv), *adj.* 1. having the quality or function of protecting: *a protective covering.* 2. tending to protect. 3. *Econ.* of, pertaining to, or designed to favor protectionism: *protective tariffs.* 4. defensive (def. 4). [1655–65; PROTECT + -IVE] —**pro·tec/tive·ly,** *adv.* —**pro·tec/tive·ness,** *n.*

protec/tive col/loid, *Physical Chem.* a lyophilic colloid added to a lyophobic sol to lessen its sensitivity to the precipitating effect of an electrolyte. [1905–10]

protec/tive colora/tion, coloration or anything likened to it that eliminates or reduces visibility or conspicuousness. [1890–95]

protec/tive custody, detention of a person by the police solely as protection against a possible attack or reprisal by someone. [1935–40]

protec/tive slope/, a slope given to a yard or the like to drain surface water away from a building.

protec/tive sys/tem, *Econ.* protectionism (def. 1). [1810–20]

pro·tec·tor (prə tek/tər), *n.* 1. a person or thing that protects; defender; guardian. 2. *Eng. Hist.* **a.** a person in charge of the kingdom during the sovereign's minority, incapacity, or absence. **b.** (*cap.*) Also called **Lord Protector.** the title of the head of the government during the period of the Protectorate, held by Oliver Cromwell (1653–58) and by Richard Cromwell, his son (1658–59). [1325–75; < LL (see PROTECT, -TOR); r. ME *protectour* < MF] —**pro·tec/tor·al,** *adj.* —**pro·tec/tor·less,** *adj.* —**pro·tec/tor·ship/,** *n.*

pro·tec·tor·ate (prə tek/tər it), *n.* 1. the relation of a strong state toward a weaker state or territory that it protects and partly controls. 2. a state or territory so protected. 3. the office or position, or the term of office, of a protector. 4. the government of a protector. 5. (*cap.*) *Eng. Hist.* the period (1653–59) during which Oliver and Richard Cromwell held the title of Lord Protector, sometimes extended to include the period of the restoration of the Rump Parliament (1659–60). [1685–95; PROTECTOR + -ATE[3]]

pro·tec·to·ry (prə tek/tə rē), *n., pl.* **-ries.** an institution for the care of destitute or delinquent children. [1650–60; PROTECT + -ORY[2]]

pro·tect·ress (prə tek/tris), *n.* a woman who guards or defends someone or something; protector. [1560–70; PROTECT(O)R + -ESS]
—**Usage.** See **-ess.**

pro·té·gé (prō/tə zhā/, prō/tə zhā/), *n.* a person under the patronage, protection, or care of someone interested in his or her career or welfare. [1780–90; < F, n. use of ptp. of *protéger* to protect < L *prōtegere.* See PROTECT]

pro·té·gée (prō/tə zhā/, prō/tə zhā/), *n.* a woman under the patronage, protection, or care of someone interested in her career or welfare. [1770–80; < F, fem. of *protégé* PROTÉGÉ]

pro·tein (prō/tēn, -tē in), *n.* 1. *Biochem.* any of numerous, highly varied organic molecules constituting a large portion of the mass of every life form and necessary in the diet of all animals and other nonphotosynthesizing organisms, composed of 20 or more amino acids linked in a genetically controlled linear sequence into one or more long polypeptide chains, the final shape and other properties of each protein being determined by the side chains of the amino acids and their chemical attachments: proteins include such specialized forms as collagen for supportive tissue, hemoglobin for transport, antibodies for immune defense, and enzymes for metabolism. 2. the plant or animal tissue rich in such molecules, considered as a food source supplying essential amino acids to the body. 3. (formerly) a substance thought to be the essential nitrogenous component of all organic bodies. —*adj.* 4. *Biochem.* of the nature of or containing protein. Also, **pro·teid** (prō/tēd, -tē id). [1835–45; < G *Protein* < Gk *prōte(ios)* primary + G *-in* -IN[2]; r. *proteine* < F] —**pro·tein·a·ceous** (prōt/ə nā/shəs, -tē i nā/-), **pro·tein/ic, pro·tei/nous,** *adj.*

pro·tein·ase (prō/tē nās/, -nāz/, -tē i-), *n. Biochem.* any of a group of enzymes that are capable of hydrolyzing proteins. [1925–30; PROTEIN + -ASE]

pro/tein coat/, *Microbiol.* capsid.

pro·tein·oid (prō/tē noid/, -tē ə-), *n. Biochem.* a polymer of amino acids resembling a biological polypeptide but formed abiotically: suggested as a possible intermediate in protein development during primitive earth conditions. [1955–60; PROTEIN + -OID]

pro/tein syn/thesis, *Biochem.* the process by which amino acids are linearly arranged into proteins through the involvement of ribosomal RNA, transfer RNA, messenger RNA, and various enzymes.

pro·tein·u·ri·a (prō/tē nŏŏr/ē ə, -nyŏŏr/-, -tē ə-), *n. Pathol.* the presence of abnormally large amounts of ... ting from kidney dis... excessive exercise, or ...5; < NL; see PROTEIN,

...rē/), *Latin.* 1. temporarily; for the time being. 2. temporary.

pro·tend (prō tend/), *Archaic.* —*v.t.* 1. to stretch forth. 2. to extend in duration. —*v.i.* 3. to stretch forward. [1400–50; late ME *protenden* < L *prōtendere* to stretch out, extend, equiv. to *prō-* PRO-[1] + *tendere* to stretch; see TEND[1]]

pro·ten·sive (prō ten/siv), *adj. Archaic.* extended in dimension or extended in time. [1635–45; < L *prōtēns(us)* (ptp. of *prōtendere* to PROTEND) + -IVE, on the model of EXTENSIVE, INTENSIVE, etc.] —**pro·ten/sive·ly,** *adv.*

pro·te·o·gly·can (prō/tē ō glī/kan), *n. Biochem.* a macromolecule composed of a polysaccharide joined to a polypeptide and forming the ground substance of connective tissue. [1969; PROTE(IN) + -O- + GLYC- + -an, var. of -ANE]

pro·te·ol·y·sis (prō/tē ol/ə sis), *n. Biochem.* the breaking down of proteins into simpler compounds, as in digestion. [1875–80; *proteo-* (comb. form repr. PROTEIN) + -LYSIS] —**pro·te·o·lyt·ic** (prō/tē ə lit/ik), *adj.*

pro·te·ose (prō/tē ōs/), *n. Biochem.* any of a class of soluble compounds derived from proteins by the action of the gastric juices, pancreatic juices, etc. [1885–90; PROTE(IN) + -OSE[2]]

protero-, a combining form meaning "earlier," "before," "former," used in the formation of compound words: *proterotype.* Also, esp. *before a vowel,* **proter-.** Cf. **proto-.** [< Gk, comb. form repr. *próteros,* comp. formed from *pró;* see PRO-[2]]

prot·er·o·type (prot/ər ə tīp/, prō/tər-), *n.* a primary type. [PROTERO- + TYPE]

Prot·er·o·zo·ic (prot/ər ə zō/ik, prō/tər-), *Geol.* —*adj.* 1. noting or pertaining to the latter half of the Precambrian Era, from about 2.5 billion to 570 million years ago, characterized by the appearance of bacteria and marine algae; Algonkian. —*n.* 2. the Proterozoic division of geologic time or the rock systems formed then; Algonkian. See table under **geologic time.** [1905–10; PROTERO- + ZO- + -IC]

pro·test (*n.* prō/test; *v.* prə test/, prō/test), *n.* 1. an expression or declaration of objection, disapproval, or dissent, often in opposition to something a person is powerless to prevent or avoid: *a protest against increased taxation.* 2. *Com.* **a.** a formal notarial certificate attesting the fact that a check, note, or bill of exchange has been presented for acceptance or payment and that it has been refused. **b.** the action taken to fix the liability for a dishonored bill of exchange or note. 3. *Law.* **a.** (upon one's payment of a tax or other state or city exaction) a formal statement disputing the legality of the demand. **b.** a written and attested declaration made by the master of a ship stating the circumstances under which some damage has happened to the ship or cargo, or other circumstances involving the liability of the officers, crew, etc. 4. *Sports.* a formal objection or complaint made to an official.
—*v.i.* 5. to give manifest expression to objection or disapproval; remonstrate. 6. to make solemn or earnest declaration. —*v.t.* 7. to make a protest or remonstrance against; object to. 8. to say in protest or remonstrance. 9. to declare solemnly or earnestly; affirm; assert. 10. to make a formal declaration of the nonacceptance or nonpayment of (a bill of exchange or note). 11. *Obs.* to call to witness. [1350–1400; (n.) ME < MF (F *protêt*), deriv. of *protester* to protest < L *prōtestārī* to declare publicly, equiv. to *prō-* PRO-[1] + *testārī* to testify, deriv. of *testis* a witness; (v.) late ME *protesten* < MF *protester*] —**pro·test/er, pro·tes/tor,** *n.* —**pro·test/a·ble,** *adj.* —**pro·test/ive,** *adj.* —**pro·test/ing·ly,** *adv.*
—**Syn.** 5. complain. 6. asseverate, avow, aver, attest. See **declare.** —**Ant.** 1. approval. 5. approve.

Prot·es·tant (prot/ə stənt or, *for 4, 6,* prə tes/tənt), *n.* 1. any Western Christian who is not an adherent of a Catholic, Anglican, or Eastern church. 2. an adherent of any of those Christian bodies that separated from the Church of Rome during the Reformation, or of any group descended from them. 3. (originally) any of the German princes who protested against the decision of the Diet of Speyer in 1529, which had denounced the Reformation. 4. (*l.c.*) a person who protests. —*adj.* 5. belonging or pertaining to Protestants or their religion. 6. (*l.c.*) protesting. [1530–40; < G or F, for L *prōtestantēs,* pl. of prp. of *prōtestārī* to bear public witness. See PROTEST, -ANT]

Prot/estant Epis/copal Church/. See **Episcopal Church in America.**

Prot/estant eth/ic. See **work ethic.** Also called **Prot/estant work/ eth/ic.** [1925–30]

Prot·es·tant·ism (prot/ə stən tiz/əm), *n.* 1. the religion of Protestants. 2. the Protestant churches collectively. 3. adherence to Protestant principles. [1640–50; PROTESTANT + -ISM]

Prot·es·tant·ize (prot/ə stən tīz/), *v.t.,* **-ized, -iz·ing.** to convert or cause to conform to Protestantism. Also, *esp. Brit.,* **Prot/es·tant·ise/.** [1825–35; PROTESTANT + -IZE]

Prot/estant Reforma/tion, reformation (def. 2).

prot·es·ta·tion (prot/ə stā/shən, prō/te-, -te-), *n.* 1. the act of protesting or affirming. 2. a solemn or earnest ... 3. formal expression or

Pro·te·us (prō/tē əs, -ty... god, son of Oceanus and ... assume different forms a... thing that readily change... ples, etc. 3. (*l.c.*) *Bacter...* aerobic bacteria of the g... as pathogens in the gas... tracts of humans.

pro·tha·la·mi·on (pr... -mi·a (-mē ə). a song ... marriage. [1597; PRO-[2] ... mund Spenser]

pro·tha·la·mi·um (p... (-mē ə). prothalamion.

pro·thal·li·um (prō ... (-thal/ē ə). 1. *Bot.* the ... plants. 2. the analogo... seed-bearing plants. [1... *thallion,* dim. of *thallo...* **thal/li·al, pro·thal/lic,** ... *adj.* —**pro·thal/loid,** ...

pro·thal·lus (prō thal... prothallium. [1850–55; ...

proth·e·sis (proth/ə s... 1. the addition of a sou... a word, as in Spanish ... 2. *Eastern Ch.* **a.** Also ... tion and preliminary ... ments. **b.** the table on ... the sanctuary or bema ... cap.) *Gk. Antiq.* a rep... in state. [1665–75; < ... fore. See PRO-[2], THESIS ... —**pro·thet/i·cal·ly,** ...

pro·thon·o·tar·y (p... *n., pl.* **-tar·ies.** 1. ... courts of law. 2. Ro... members of the col... charged chiefly with ... canonizations. **b.** an ... prelates. 3. *Gk. Orth...* triarch of Constantin... late ME < ML *prōth...* *prōtonotārios.* See PR... **al** (prō thon/ə târ/ē ...

prothon/otary ap... ostolic. a member ... Roman Curia. [1545...

prothon/otary wa... *taria citrea,* of the e... head and underpart... [1780–90, *Amer.*; so ... bles the robes tradit...

prothorac/ic glan... glands in the anteric... to promote the seri... hood. [1885–90]

pro·tho·rax (prō t... **-tho·ra·ces** (-thôr/... of the thorax of an ... [1820–30; < NL; s... (prō/thō ras/ik, -th...

pro·throm·bin (p... protein involved in ... by factors in the p... called **thrombogen...**

pro·tist (prō/tist), ... isms, classified in ... free-living or aggr... have diverse repro... ing the protozoans ... some classificatio... the more primitive ... distribute the org... and Animalia ac... [1885–90; < NL *P...* < Gk *prṓtistos* (... *prōtos* first; see PR... *n.* —**pro·tis/tic,** ...

Pro·tis·ta (prō t... a taxonomic king... < NL; see PROTIS...

pro·tis·tol·o·gy ... Protista. [1910–... **to·log·i·cal** (prō ... **gist,** *n.*

pro·ti·um (prō/... and most comm... [1930–35; PROT- ...

proto-, a combi... "earliest form o... words (*protomar...* in chemical term... compounds, or t... of an element. ... comb. form rep... see PRO[2]-]

pro·to·ac·tin·i... protactinium.

APPENDIX II

Copy of Reference

Sara et al.

The Biological Role of Truncated Insulin-like Growth Factor-1

and the Tripeptide GPE in the Central Nervous System

The Biological Role of Truncated Insulin-like Growth Factor-1 and the Tripeptide GPE in the Central Nervous System[a]

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INTRODUCTION

Since early in this century, attempts have been made to identify substances present in serum and organ extracts that are capable of promoting the growth of the nervous system. Today several such growth-promoting factors have been isolated and identified, such as nerve growth factor (NGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and insulin-like growth factors (IGFs). It has become clear that these growth factors are endogenously produced within the developing nervous system at specific growth phases and that they interact to regulate the growth and development of the central nervous system (CNS). A role for the IGFs in the regulation of CNS growth was first implicated 20 years ago by the finding that growth hormone had an indirect action on brain growth which was believed to be mediated by the production of a brain growth factor from either the placenta or the fetus.[1,2]

[a]These studies have been supported by the Swedish Medical Research Council, Ostergren Fund, Swedish Cancer Foundation, and the Cancer Fund in Stockholm.

TRUNCATED IGF-1 AND GPE

A bioassay to determine fetal brain cell DNA synthesis[3] and later a radioreceptor assay using fetal brain plasma membranes[4] were developed to isolate the brain growth factor from human fetal brain tissue. Partial amino acid sequencing revealed the brain growth factor to be identical to IGF-1 over the first 29 amino acids, but to have a truncated aminoterminus lacking the first three amino acids of IGF-1 (FIGURE 1).[5] The carboxyl-terminal amino acid was shown to be identical to that of IGF-1. An identical truncated IGF-1 was subsequently isolated from the adult human brain.[6] Intact IGF-1 could not be detected in either the fetal or the adult human brain. The formation of truncated IGF-1 or -3N-IGF-1 appeared to be specific to the tissue extract since only intact IGF-1 was isolated from serum when the same purification process was used.

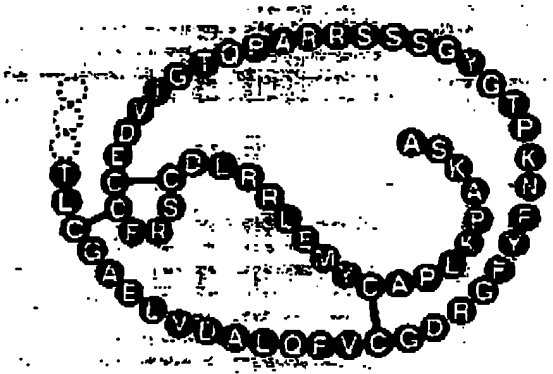

FIGURE 1. Amino acid sequence of human truncated IGF-1 (-3N-IGF-1). The single letter amino acid code is used. The protein lacks the aminoterminal tripeptide GPE. Truncated IGF-1 has been identified in human brain, human platelets, porcine uterus, and bovine colostrum.

The possibility of further structural modifications in the brain IGF could not be discounted at that time since the purified peptide displayed greatly enhanced neurotrophic activity compared to IGF-1. The complete amino acid sequence of the peptide has now been deduced from the nucleotide sequence of human fetal brain IGF-1 cDNA.[7] Using reverse transcriptase polymerase chain reaction (RT-PCR) to amplify cDNA obtained from isolated human fetal brain, two cDNA sequences encoding precursor proteins that correspond to IGF-1a and IGF-1b were obtained. Thus the amino terminal truncation of the IGF-1 protein represents the only sequence difference in the brain IGF-1 (FIGURE 1). The brain truncated IGF-1 most likely arises from posttranslational modification of the IGF-1 precursor protein. As yet it is unclear as to whether the precursor to truncated IGF-1 is the a or b form of the IGF-1 prohormone. Recently, the amino terminal tripeptide of IGF-1, namely, glycyl-prolyl-glutamate (GPE), has been identified in human brain. Thus there are two protein products from expression of the IGF-1 gene in the human brain, namely, truncated IGF-1 and the tripeptide GPE.

The presence of IGF-1 in the nervous system appears to be a phylogenetically ancient phenomenon. Using immunological methods, IGF-1 has been localized in the nervous system as well as the gut of lower vertebrates, including bony and cartilaginous fish and cyclostomi, as well as protochordates. For example, IGF-1 immunoreactive perikarya and fibers have been observed in all levels of the brain of the Atlantic hagfish, *Myxine glutinosa*.[8] IGF-1-like immunoreactivity has also been localized in central neurones of the urochordate *Ciona intestinalis* and the cephalochordate *Branchiostoma lanceolatum*.[9] Thus the presence of IGF-1 in the "brain-gut axis" has been well preserved during vertebrate evolution. The identity of the IGF-1-like molecule in the brain-gut axis of the lower vertebrates and protochordates remains to be determined. The nucleotide sequence of an IGF cDNA isolated from *Myxine glutinosa* showed 70% homology to the A and B domains of both human IGF-1 and IGF-2,[10] and a hybrid insulin/IGF cDNA related to both human insulin and IGFs has been cloned from *Branchiostoma californiensis*.[11] Chan *et al.* have proposed that the latter hybrid molecule represents the transitional form prior to insulin and IGF divergence at an early stage of vertebrate evolution.[11] It is of interest that the deduced amino acid sequence of the hybrid insulin/IGF molecule reveals a different aminoterminal dipeptide compared to mammalian IGF-1. A plasma membrane receptor similar to that of mammalian IGF-1 receptor has also been identified in the nervous system of lower vertebrates, including *Myxine glutinosa*.[12]

The truncated IGF-1 has been identified in several tissues (FIGURE 1). Ogasawara *et al.* identified truncated IGF-1 in porcine uterus where the peptide accounted for the complete mitogenic activity of uterine extracts.[13] Truncated IGF-1 has also been isolated from human platelets.[14] Lysates of human platelets contain intact as well as truncated IGF-1 and IGF-2. IGF-1 was released from the platelets during degranulation, suggesting a role in wound healing.[15] Francis *et al.* have identified truncated IGF-1 in bovine colostrum where intact IGF-1 was additionally found to be present.[16] In all studies during its purification, truncated IGF-1 displayed enhanced biological activity. With the availability of synthetic and recombinant truncated IGF-1, the reason for this enhanced biological potency became apparent. Truncated IGF-1 binds only weakly to the IGF binding proteins (IGFBPs).[17–20] Although truncated IGF-1 shows some binding to IGFBP-3, a marked reduction in binding affinity to IGFBP-1, -2, -6 has been found in comparison to intact IGF-1 (less than 1%). Analogues of IGF-1 with substitutions in the aminoterminus pentapeptide have identified Glu in residue 3 as playing a significant role in IGFBP binding. In a wide variety of cultured cells, it has been demonstrated that the enhanced biological activity of the truncated IGF-1 is most likely due to its failure to be bound by IGFBPs which can compete with the IGF-1 receptor and attenuate the biological activity of IGF-1. Thus the failure to bind to IGFBPs results in a greater availability of truncated IGF-1 to the target cell receptors (FIGURE 2).

BIOLOGICAL ACTION IN CNS

Truncated IGF-1 (-3N:IGF-1) and the tripeptide GPE display separate biological functions in the nervous system which are mediated via distinct receptors on their target cells. Truncated IGF-1 has a potent neurotrophic action via interaction in the IGF-1 receptor in the CNS. The IGF-1 receptor is widely distributed throughout the CNS,[21] and its expression is enhanced during the rapid growth phase of early life.[22] IGF-1's neurotrophic action predominates during early development, when the IGFs regulate the growth and differentiation of the nervous system. *In vitro* studies have demonstrated that IGF-1 stimulates the proliferation of neuroblast and glioblast

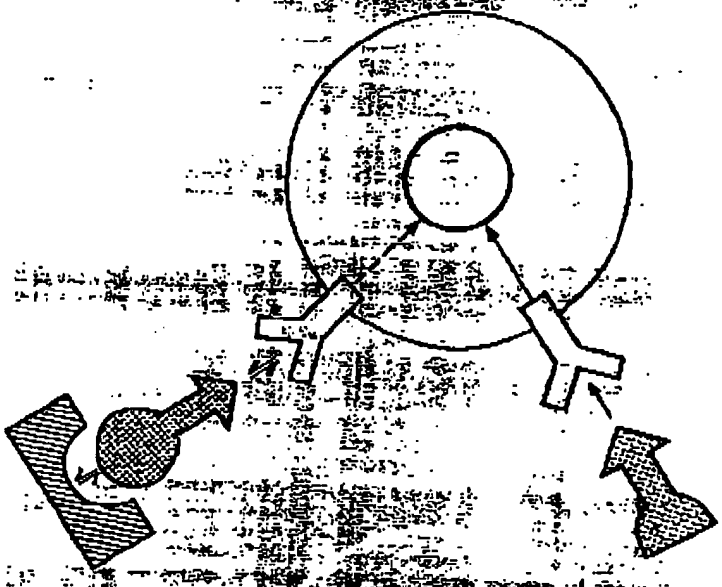

FIGURE 2. Model to account for the enhanced neurotrophic activity of truncated IGF-1 compared to intact IGF-1. Failure to become associated with the IGFBPs is hypothesized to result in greater availability of truncated IGF-1 to the IGF-1 receptors on target cells.

precursor cells, as well as their differentiation.[23] Several studies indicate that IGF-1 may play an important role in synapse formation and myelination.[24-27] Comparison between the various IGFs reveals that truncated IGF-1 displays a far greater neurotrophic activity compared to intact IGF-1 or IGF-2. Using fetal brain cells *in vitro*, Carlsson-Skwirut *et al.* showed that this enhanced neurotrophic potency was due to failure of truncated IGF-1 to bind to binding proteins.[28] The addition of IGFBP-1 to the culture medium could inhibit the stimulation of fetal brain cell DNA synthesis by intact IGF-1 but had no effect on the action of truncated IGF-1. A similar action has been observed with intracellular transplantation of brain tissue by Giacubini *et al.*[29] Truncated IGF-1 had a potent growth-promoting action on parietal cortex and spinal cord grafts transplanted into the anterior chamber of the eye of adult rats. This *in vivo* model allows for direct observation of graft survival and growth. The action of truncated IGF-1 was developmentally as well as regionally specific. For example, a significant growth-promoting action was observed on spinal cord grafts at embryonic day E14 but not at E16. It was suggested that these differences reflected the stage of receptor maturation and function in the various regions. This is in accordance with the expression of the IGF-1 gene in specific cell populations at discrete times during CNS development.[30] Intact IGF-1 failed to stimulate the growth of brain transplants, presumably due to the presence of IGFBPs which were present in the vitreous fluid.

Similarly, when administered intravenously, truncated IGF-1 displays reduced binding to IGFBPs in the circulation.[31] The truncated form is more rapidly cleared

from the blood[32] and is also degraded faster than intact IGF-1.[31] Consequently, the acute hypoglycemic effect of truncated IGF-1 is greater than that of intact IGF-1.[3] Increased degradation due to low association with IGFBPs most likely explains the failure to observe any significant enhancement in growth following the subcutaneous administration of truncated IGF-1 to neonatal rats in spite of enhancement being observed following intact IGF-1 administration. In contrast to the growth of normal rats, enhanced growth has been observed in growth-hormone-deficient lit/lit mouse following truncated IGF-1 administration.[33] Truncated IGF-1 has similarly been reported to be more potent than intact IGF-1 in regulating nitrogen balance and muscle protein metabolism in nitrogen-restricted rats.[34]

The aminoterminal tripeptide of IGF-1, GPE, displays a different range of biological actions compared to truncated IGF-1.[35] These effects are not mediated by IGF receptors. As shown in FIGURE 3, GPE fails to cross-react in the IGF-1 receptor and does not influence the binding of either intact or truncated IGF-1 to this receptor. The tripeptide similarly fails to cross-react in the IGF-2 receptor. GPE does not bind to IGFBPs nor does it influence the association of the IGFs to their binding proteins. Extensive *in vivo* studies have not revealed any growth-promoting activity of GPE. The results of one such study are summarized in FIGURE 4. Growth was followed in rats receiving 30 μg GPE subcutaneously (sc) per day from days 3 to 15 of postnatal life. As shown in FIGURE 4, no significant growth effects, including tail length and organ weights, were observed. However at maturity, the animals receiving GPE during this preweaning period displayed a significant increase in activity measurements in an open field test. It has since been demonstrated that GPE plays a neuromodulatory role in the CNS,[35] which may account for the changes in activity observed in the GPE-treated rats.

The structure of GPE suggested that it may interact in receptors for glutamate which is a major excitatory amino acid neurotransmitter in the CNS. Using rat synaptic membranes, it was shown that GPE cross-reacted in the *N*-methyl-D-

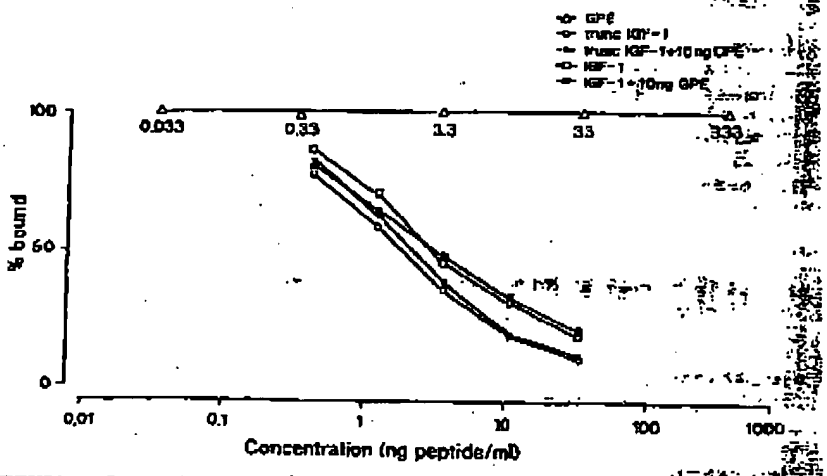

FIGURE 3. Competition with ^{125}I-IGF-1 for binding to human fetal brain membranes. Data are expressed as the percentage bound in the absence of competing peptide. –

aspartate (NMDA) but not the kainate or quisqualate type of glutamate receptor.[35] While the carboxyl terminal glutamate was necessary for NMDA receptor binding, the aminoterminal glycine potentiated this ionic reaction. Glycine has earlier been shown to potentiate responses mediated via the NMDA receptor and has been suggested to be a specific regulator of the NMDA receptor via binding to an allosteric site.[36] GPE facilitates the release of dopamine from cortical slices. As shown by the use of a selective competitive antagonist, this action is mediated via interaction in the NMDA receptor.[35] In addition, GPE has a potent stimulatory action on acetylcholine release from cortical neurones.[33,37] This action cannot be inhibited by NMDA receptor blocking agents, and acetylcholine potentiation is mediated via an as yet unidentified receptor. GPE does not interact with choline uptake sites or muscarinic receptors on neurones. Although GPE interacts in nicotinic binding sites in the rat cortex, this interaction occurs at a concentration several orders of magnitude greater than that required to potentiate acetylcholine release. Thus the receptor mechanism for acetylcholine potentiation remains to be identified. It had been reported earlier that intact IGF-1 potentiates acetylcholine release from cortical slices.[38] Similarly, GPE has been reported to enhance catecholamine release from chromaffin cells.[39] Since truncated IGF-1 fails to enhance acetylcholine release from the cortical slices,[37] it may be suggested that the action of intact IGF-1 on neurotransmitter release was due to the tripeptide GPE. However, during this acute experiment, significantly less truncated IGF-1 was taken up by the cortical slices during the 30-minute incubation period. Thus, in the adult cortex, formation of the IGFBP complex may be necessary for transport across the microvascular barrier to directly interact with neurones and induce an acute action.

Neuronal activity can be modulated by GPE. This has been demonstrated in single cortical neurones following iontophoretic application of GPE. As shown in FIGURE 5, GPE alone has no effect on the electrophysiological activity of the neurone; however, when applied together with glutamate, it potentiates the action of

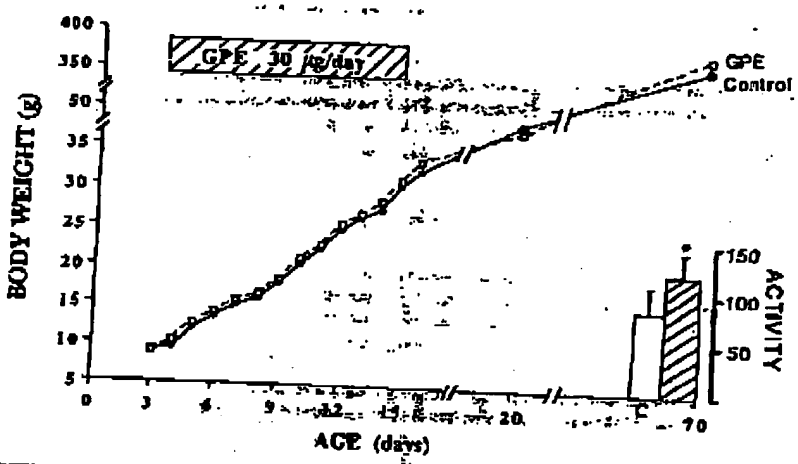

FIGURE 4. The growth of rats receiving either 30 µg GPE sc/day or vehicle alone from days 3 to 15 of postnatal life. No significant effect on body weight was observed. At 70 days of age, open field behavior was examined. GPE-treated rats displayed a significant increase in activity scores.

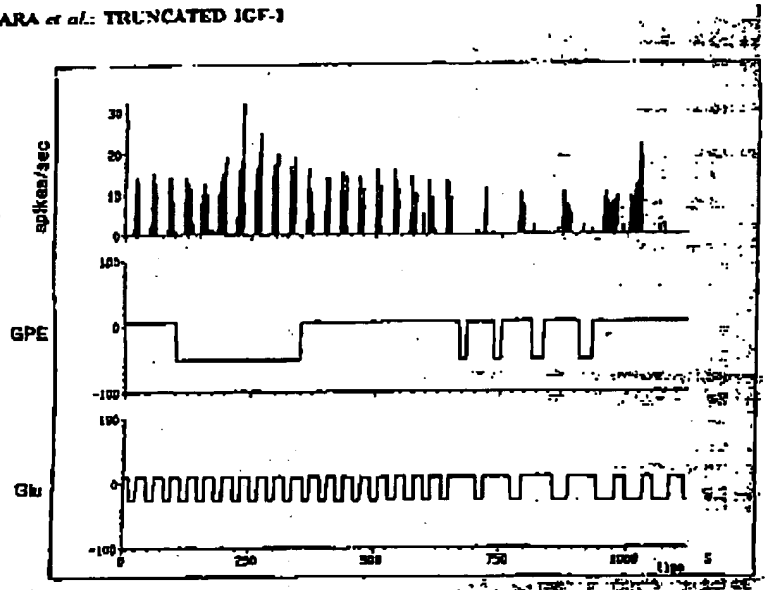

FIGURE 5. Cortical neurone electrophysiological activity following microiontophoretic app cation of GPE. The effect of GPE on spontaneous as well as glutamate-driven single cell activi determined as spikes/second is shown.

the glutamate-driven neurone. Similarly, in the spinal cord, GPE has no direc influence on motor neurone activity when applied intrathecally; however GP potentiates the facilitated spinal cord reflex in response to other stimuli.

CONCLUSION

Thus there are at least two protein products from expression of the IGF-1 gene i the CNS. These proteins result from posttranslational modification of the IGF- precursor protein. Truncated IGF-1 (-3N:IGF-1) acts as a potent neurotrophi factor and this action is mediated via the IGF-1 receptor. The tripeptide GPI appears to have a quite different CNS function, namely, the modulation of neurotrans mitter release. This potentiating action is mediated at least in part via interaction a the NMDA receptor. This is the first example of a product from a growth factor gen being involved in neurotransmission in the CNS. A similarly novel role for the neurotransmitter acetylcholine has been suggested in the regulation of brain growth.

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